EXHIBIT 2

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

K.C., et al., Plaintiffs, v. THE INDIVIDUAL MEMBERS OF THE MEDICAL LICENSING BOARD OF INDIANA, in their official capacities, et al., Defendants.	No. 1:23-cv-00595-JPH-KMB

DEFENDANTS' DISCLOSURE OF EXPERT REPORT OF PAUL W. HRUZ, M.D., PH.D

Pursuant to 28 U.S.C. § 1746, I declare:

1. I have been retained by counsel for Defendants as an expert witness in connection with the above-captioned litigation. I have actual knowledge of the matters stated in this report. My professional background, experience, and publications are detailed in my curriculum vitae. A true and accurate copy of my CV is attached as Exhibit A to this report.

2. I am an Associate Professor of Pediatrics in the Division of Pediatric Endocrinology and Diabetes at Washington University School of Medicine. I also

have a secondary appointment as Associate Professor of Cellular Biology and Physiology in the Division of Biology and Biological Sciences at Washington University School of Medicine. I served as Chief of the Division of Pediatric Endocrinology and Diabetes at Washington University from 2012-2017. I served as the Director of the Pediatric Endocrinology Fellowship Program at Washington University from 2008-2016. I am currently serving as Associate Fellowship Program Director at Washington University in St. Louis.

3. Related to the litigation of issues of sex and gender, I have been designated as an expert witness in *Carcaño v. Cooper* (United States District Court for the Middle District of North Carolina, Case No. 1:16-cv-236); *Doe v. Board of Education of the Highland School District* (United States District Court for the Southern District of Ohio, Eastern Division, Case No. 2:16-CV-524); *Whitaker v. Kenosha Unified School District* (United States District Court for the Eastern District of Wisconsin, Case No. 2:16-cv-00943), *Bruce v. South Dakota* (United States District Court for the District of South Dakota, Western Division, Case No. 17-5080); *Kadel v. Falwell* (United States District Court for the Middle District of North Carolina, Case No. 1:19-cv-272-LCB-LPA); *Brandt v. Rutledge* (United States District Court for the Eastern District of Arkansas, Central Division, Case No. 4:21-CV-00450-JM); *D.H. v. Snyder* (United States District Court for the District of Arizona, Case No. 4:20-cv-00335-SHR), Cause DF-15-09887-SD of the 255th Judicial Circuit of

Dallas County, TX regarding the dispute between J.A. D.Y. and J.U. D.Y., Children; *Dekker v. Weida* (United States District Court for the Northern District of Florida, Tallahassee Division, Case No. 4:22-cv-00325-RH-MAF); and *Boe v. Marshall* (United States District Court for the Middle District of Alabama Northern Division, Civil Action No. 2:22-cv-184-LCB). I have also served as a science consultant or submitted written testimony for court cases in Canada (B.C. Supreme Court File No. E190334) and Great Britain (*Bell v. Tavistock*).

4. I am being compensated at an hourly rate for actual time devoted, at the rate of $400 per hour including report drafting, travel, testimony, and consultation. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I provide. If called to testify in this matter, I would testify truthfully and based on my expert opinion.

5. My opinions as detailed in this report are based upon my:

a. knowledge, training, and clinical experience in caring for thousands of patients over many years;
b. detailed methodological reviews of hundreds of relevant peer-reviewed science publications;
c. consults, discussions, and team analyses with colleagues and other experts in the field, including attendance and participation in various professional conferences;
d. publications in peer-reviewed scientific journals;
e. editorial work for peer-reviewed scientific journals; and
f. peer-reviewed research grant receipt and review work.

In addition, I have reviewed the expert reports in this case of Dr. Dan Karasic, Dr. Daniel Shumer, and Dr. Jack Turban. The materials that I have relied upon are the

same types of materials that other experts in my field of clinical practice rely upon when forming opinions on the subject, including hundreds of published, peer-reviewed scientific research (and professional) articles.

6. My opinions and hypotheses in this matter are — as all expert reports — subject to the limitations of documentary and related evidence, the impossibility of absolute predictions, and the limitations of social, biological, and medical science. I have not met with, or personally interviewed, anyone in this case. I have not yet reviewed all of the evidence in this case and my opinions are subject to change at any time as new information becomes available to me. Only the trier of fact can determine the credibility of witnesses and how scientific research may or may not be related to the specific facts of any particular case. In my opinion, a key role of an expert witness is to help the court, lawyers, parties, and the public understand and apply reliable scientific, technical, and investigative principles, hypotheses, methods, and information.

BACKGROUND

7. I received my Doctor of Philosophy degree from the Medical College of Wisconsin in 1993. I received my Medical Degree from the Medical College of Wisconsin in 1994.

8. I am board certified in Pediatrics and Pediatric Endocrinology. I have been licensed to practice medicine in Missouri since 2000. My professional memberships include the American Diabetes Association, the Pediatric Endocrine Society, and the Endocrine Society.

9. I have published 63 scholarly articles over my academic career spanning over two decades. This includes peer-reviewed publications in the leading journals in the fields of metabolism, cardiology, HIV, and ethics. Those journals include Gastroenterology, Circulation, Diabetes, Science Signaling, the Journal of Biological Chemistry, and FASEB Journal. See Exhibit A.

10. I have served as a Reviewer for a number of leading science journals in relevant fields including the Journal of Clinical Endocrinology and Metabolism, the Journal of Biological Chemistry, Diabetes, Scientific Reports, and PLOS ONE, assessing the quality of evidence that is put forward for publication. I have also been involved in the evaluation of clinical trials with colleagues. I have received over $4.6 million in governmental and non-governmental funding for scientific research, including grants from the National Institutes of Health, the American Diabetes Association, The American Heart Association, the March of Dimes, and the Harrington Discovery Institute. I am a member of the Alpha Omega Alpha Medical Honor Society and have received the Armond J. Quick Award for Excellence in Biochemistry,

the Eli Lilly Award for Outstanding Contribution to Drug Discovery, and the Julio V. Santiago Distinguished Scholar in Pediatrics Award.

11. During the more than 22 years that I have been in clinical practice, I have participated in the care of hundreds of infants and children, including adolescents, with disorders of sexual development. I was a founding member of the multidisciplinary Disorders of Sexual Development (DSD) program at Washington University. I continue to contribute to the discussion of complex cases and the advancement of research priorities in this field. In the care of these patients, I have acquired expertise in the understanding and management of associated difficulties in gender identification and gender transitioning treatment issues. I have trained and/or supervised hundreds of medical students, residents, and clinical fellows in the practice of medicine.

12. In my role as a scientist and as the Director of the Division of Pediatric Endocrinology at Washington University, I extensively studied the existing scientific research literature related to the incidence, potential etiology, and treatment of gender dysphoria as efforts were made to develop a Transgender Medicine Clinic at Saint Louis Children's Hospital. I have participated in local, national, and international meetings where the endocrine care of children with gender dysphoria has been discussed in detail and debated in depth. I have met individually and consulted with

several pediatric endocrinologists (including Dr. Norman Spack) and other professionals specializing in sexual health (including Eli Coleman) who have developed and led transgender programs in the United States. I have also consulted with, met with, and had detailed discussions with dozens of parents of children with gender dysphoria to understand the unique difficulties experienced by this patient population. I continue to evaluate the ongoing experimental investigation of this condition. I am frequently consulted by other medical professionals to help them understand the complex medical and ethical issues related to this emerging field of medicine.

13. In my clinical practice, I have cared for children from birth to the completion of college in their early twenties who have a variety of hormone-related diseases. This includes disorders of growth, puberty (both precocious and delayed), glucose homeostasis (both hypoglycemia and diabetes mellitus), adrenal function (both adrenal insufficiency and steroid excess), thyroid function, skeletal abnormalities, gonadal dysfunction (including polycystic ovarian syndrome and ovarian failure), hypopituitarism, and disorders of sexual development. Pediatric patients referred to our practice for the evaluation and treatment of gender dysphoria are cared for by an interdisciplinary team of providers that includes a psychologist and pediatric endocrinologist who have been specifically chosen for this role based upon a special interest in this patient population.

BACKGROUND ON SEX AND GENDER

14. Sex is an objective biological trait intrinsically oriented toward specific roles in the conception and development of new members of a species. Both males and females contribute genetic information in distinct yet complementary ways. Males have the role of delivering sperm produced by testes and the unique paternal DNA contained therein to a female. Females have the role of receiving this male genetic information to join with the maternal genetic information contained in ova produced by ovaries. Sex is not "assigned at birth"; it is permanently determined by biology at conception. This remains the standard definition that has been accepted by the relevant scientific community and used worldwide by scientists, medical personnel, and society in general for decades.[1]

15. The scientific and clinical measurement of sex is done with highly reliable and valid objective methodologies. Visual medical examination of the appearance of the external genitalia is the primary methodology used by clinicians to recognize sex. In cases where genital ambiguity is present, additional testing modalities including chromosomal analysis, measurement of hormone levels, radiographic imaging of internal sexual anatomy and biological response to provocative testing are utilized. The measurement and assessment of biological sex has been documented

[1] See Miller LR, et al. Considering sex as a biological variable in preclinical research. FASEB J. 2017 Jan;31(1):29-34; Clayton JA. Studying both sexes: a guiding principle for biomedicine. FASEB J. 2016 Feb;30(2):519-24.

by valid and reliable research published in credible journals, and is accepted by the relevant scientific community. Medical recognition of an individual as male or female is correctly made at birth in nearly 99.98% of cases according to external phenotypic expression of primary sexual traits (i.e., the presence of a penis for males and presence of labia and vagina for females). [2]

16. For members of the human species (and virtually all mammals), sex is normatively aligned in a binary fashion (i.e., either male or female) in relation to biologic purpose. The presence of individuals with disorders of sexual development (along the range of the established Prader scale) does not alter this fundamental reality.

17. Due to genetic and hormonal variation in the developing fetus, normative development of the external genitalia in any individual differs with respect to size and appearance while maintaining an ability to function with respect to biologic purpose (i.e., reproduction). Internal structures (e.g., gonad, uterus, vas deferens) normatively align in more than 99.9%+ of mammals with external genitalia, including humans.

[2] See L. Sax, How common is Intersex? A response to Anne Fausto-Sterling, 39 J. Sex Rsch. 174 (2002).

18. Due to the complexity of the biological processes that are involved in normal sexual development, it is not surprising that a very small number of individuals are born with defects in this process (1 in 5,000 births).[3] Defects can occur through either inherited or *de novo* mutations in genes that are involved in sexual determination or through environmental insults during critical states of sexual development. Persons who are born with such abnormalities are considered to have a disorder of sexual development (DSD). Most often, this is first detected as ambiguity in the appearance of the external genitalia. Such detection measurements are reliable and valid and accepted by the relevant scientific community.

19. The medical care of persons with DSDs is primarily directed toward identification of the etiology of the defect and treatment of any associated complications. Similar to the diagnosis of other diseases, objective diagnostic tools such as the Prader scale are used to assess, measure, and assign a "stage" to the severity of the deviation from normal. In children with DSDs, characterization based upon phenotype alone does not reliably predict the sex chromosomes present, nor does it necessarily correlate with potential for biological sexual function. The need for making a tentative sex assignment is unique to children with a DSD and does not apply to individuals with normally formed and functional genitalia at birth. Deci-

[3] Ibid

sions on initial sex assignment in these very rare DSD cases require detailed assessment of objective, reliable medical evidence by a team of expert medical providers. In previous years, the general practice was to make a definitive sex assignment shortly after birth, the belief being that this would allow patients with a disorder of sexual development to best conform to the assigned sex and parents-caregivers to help socialize the child to the assigned sex. Current practice is to defer sex assignment until the etiology of the disorder is determined and, if possible, a reliable prediction can be made on likely biologic and psychologic outcomes. When this cannot be done with confidence, a presumptive sex assignment is made. Factors used in making such decisions include karyotype (46XX, 46XY, or other), phenotypic appearance of the external genitalia, and parental desires. The availability of new information can, in rare circumstances, lead to a change in sex determination. Decisions on whether to surgically alter the external genitalia to align with sex are generally deferred until the patient is able to provide consent.[4] The tentative assignment of sex is unique to individuals with a DSD.

20. "Gender," a term that had traditionally been reserved for grammatical purposes, is currently used to describe the psychological and cultural characteristics of a person in relation to biological sex. Gender in such new definitions therefore

[4] See P. A. Lee et al., Global Disorders of Sex Development Update since 2006: Perceptions, Approach and Care, 85 Horm. Rsch. Paediatr. 158 (2016).

exists only in reference to subjective personal perceptions and feelings and societal expectations, not biology. The reliability and validity of various usages of the term "gender" is currently controversial. The dangers of incorrectly using the term "gender" in place of "sex" have been acknowledged by the Endocrine Society.[5]

21. "Gender identity" refers to a person's individual experience and perception and unverified verbal patient reports of how they experience being male or female or a combination of these or other categories. The term "gender identity" is controversial. There is no current worldwide definition of "gender identity" accepted by the relevant clinical communities. The measurement error rate for "gender identity" is unknown.

22. People who identify as "transgender" transiently or persistently experience a sex-discordant gender identity.[6]

PUBERTY

23. Puberty is "the morphological and physiological changes that occur in the growing boy or girl as the gonads change from the infantile to the adult state. These changes involve nearly all the organs and structures of the body but they do not begin at the same age nor take the same length of time to reach completion in all

[5] See A. Bhargava et al., Considering Sex as a Biological Variable in Basic and Clinical Studies: An Endocrine Society Scientific Statement, 42 Endocrine Revs. 219 (2021).
[6] American Psychological Association, The Diagnostic and Statistical Manual of Mental Disorders, (DSM-5), 451 (2013).

individuals. Puberty is not complete until the individual has the physical capacity to conceive and successfully rear children."[7]

24. The principal manifestations of puberty are:

- The adolescent growth spurt; i.e., an acceleration followed by a deceleration of growth in most skeletal dimensions and in many internal organs.
- The development of the gonads.
- The development of the secondary reproductive organs and the secondary sex characters.
- Changes in body composition, i.e., in the quantity and distribution of fat in association with growth of the skeleton and musculature.
- Development of the circulatory and respiratory systems leading, particularly in boys, to an increase in strength and endurance.[8]

25. The ability to physically conceive children is made possible by the maturation of the primary sex characteristics, the organs and structures that are involved directly in reproduction. In boys, these organs and structures include the scrotum, testes, and penis while in girls they include the ovaries, uterus, and vagina. In addition to these primary sex characteristics, secondary sex characteristics also develop

[7] W. A. Marshall et al., Puberty, in F. Falkner et al. eds., 2 Human Growth: A Comprehensive Treatise, 2nd ed., (New York: Springer, 1986), 171.
[8] *Id.* at 171-72.

during puberty — the distinctive physical features of the two sexes that are not directly involved in reproduction. Secondary sex characteristics that develop in girls include "the growth of breasts and the widening of the pelvis," while in boys they include "the appearance of facial hair and the broadening of shoulders." Other patterns of body hair and changes in voice and skin occur during puberty in both girls and boys.[9]

26. Physicians characterize the progress of puberty by marking the onset of different developmental milestones. The earliest visible event, the initial growth of pubic hair, is known as "pubarche;" it occurs between roughly ages 8 and 13 in girls, and between ages 9.5 and 13.5 in boys.[10] In girls, the onset of breast development, known as "thelarche," occurs around the same time as pubarche.[11] "Menarche" is another manifestation of sexual maturation in females, referring to the onset of menstruation, which typically occurs at around 13 years of age and is generally a sign of the ability to conceive.[12] Roughly corresponding to menarche in girls is "spermarche" in boys; this refers to the initial presence of viable sperm in semen, which also typically occurs around 13.[13] (The "-arche" in the terms for these milestones

[9] R. V. Kail et al., Human Development: A Life-Span View 276 (7th ed. 2016).
[10] J. Stang et al., Adolescent Growth and Development 1, 2-3 in J. Stang et al. eds., Guidelines for Adolescent Nutrition Services, (2005), available at http://demoiselle2femme.org/wp-content/uploads/Adolescent-Growth-and-Development.pdf (last visited Apr. 29, 2023).
[11] *Id.* at 2.
[12] Marshall et al., Puberty, at 191-92.
[13] *Id.* at 185.

comes from the Greek for beginning or origin). Pubarche and thelarche correspond to the transition from Tanner Stage 1 to Tanner Stage 2 of sexual development. Spermarche and menarche generally occur at Tanner Stage 4 to Tanner Stage 5.

27. Scientists distinguish three main biological processes involved in puberty: adrenal maturation, gonadal maturation, and somatic growth acceleration. "Adrenarche" — the beginning of adrenal maturation — begins between ages 6 and 9 in girls, and ages 7 and 10 in boys. The hormones produced by the adrenal glands during adrenarche are relatively weak forms of androgens (masculinizing hormones) known as dehydroepiandrosterone and dehydroepiandrosterone sulfate. These hormones are responsible for signs of puberty shared by both sexes: oily skin, acne, body odor, and the growth of axillary (underarm) and pubic hair.[14]

28. "Gonadarche" — the beginning of the process of gonadal maturation — normally occurs in girls between ages 8 and 13 and in boys between ages 9 and 14.[15] The process begins in the brain, where specialized neurons in the hypothalamus secrete gonadotropin-releasing hormone (GnRH).[16] This hormone is secreted in a cyclical or "pulsatile" manner — the hypothalamus releases bursts of GnRH, and when the pituitary gland is exposed to these bursts, it responds by secreting two

[14] S. E. Oberfield et al., Approach to the Girl with Early Onset of Pubic Hair, 96 J. Clin. Endocrinol. & Metabol. 1610 (2011).
[15] S. F. Witchel et al., Puberty: Gonadarche and Adrenarche, in J. F. Strauss III et al. eds., Yen and Jaffe's Reproductive Endocrinology, 6th ed., 395, 395-446.e16 (2009).
[16] A. E. Herbison, Control of Puberty Onset and Fertility by Gonadotropin-Releasing Hormone Neurons, 12 Nature Revs. Endocrinol. 452 (2016).

other hormones.[17] These are luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate the growth of the gonads (ovaries in females and testes in males).[18] (The "follicles" that the latter hormone stimulates are not hair follicles but ovarian follicles, the structures in the ovaries that contain immature egg cells.) In addition to regulating the maturation of the gonads and the production of sex hormones, these two hormones also play an important role in regulating aspects of human fertility.[19]

29. As the gonadal cells mature under the influence of LH and FSH, they begin to secrete androgens (masculinizing sex hormones like testosterone) and estrogens (feminizing sex hormones).[20] These hormones contribute to the further development of the primary sex characteristics (the uterus in girls and the penis and scrotum in boys) and to the development of secondary sex characteristics (including breasts and wider hips in girls, and wider shoulders, breaking voices, and increased muscle mass in boys). The ovaries and testes both secrete androgens as well as estrogens, however the testes secrete more androgens and the ovaries more estrogens.[21]

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[17] *Id.* at 453.
[18] *Id.* at 454.
[19] *Id.* at 452.
[20] M. A. Preece, Prepubertal and Pubertal Endocrinology, in F. Falkner et al. eds., 2 Human Growth: A Comprehensive Treatise, 211, 212 (1986).
[21] R. A. Hess, Estrogen in the adult male reproductive tract: A review, 1 Reproductive Biol. and Endocrinol. 1, (2003); H. G. Burger, Androgen Production in Women, 77 (Suppl.) Fertility and Sterility, S3-5 (2002).

30. The gonads and the adrenal glands are involved in two separate but interrelated pathways (or "axes") of hormone signaling. These are the hypothalamic-pituitary-gonadal (HPG) axis and the hypothalamic-pituitary-adrenal (HPA) axis.[22] Though both play essential roles in puberty, it is, as just noted, the HPG axis that results in the development of the basic reproductive capacity and the external sex characteristics that distinguish the sexes.[23]

31. The third significant process that occurs with puberty, the somatic growth spurt, is mediated by increased production and secretion of human growth hormone, which is influenced by sex hormones secreted by the gonads (both testosterone and estrogen). Similar to the way that the secretion of GnRH by the hypothalamus induces the pituitary gland to secrete FSH and LH, in this case short pulses of a hormone released by the hypothalamus cause the pituitary gland to release human growth hormone.[24] This process is augmented by testosterone and estrogen. Growth hormone acts directly to stimulate growth in certain tissues, and also stimulates the liver to produce a substance called "insulin-like growth factor 1," which has growth-stimulating effects on muscle.[25]

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[22] R. D. Romeo, Neuroendocrine and Behavioral Development during Puberty: A Tale of Two Axes, 71 Vitamins and Hormones 1, 1-25 (2005).
[23] M. E. Wierman et al., Neuroendocrine Control of the Onset of Puberty, 2 Human Growth 225 (1986).
[24] M. A. Preece, Prepubertal and Pubertal Endocrinology, at 218-19.
[25] U. J. Meinhardt et al., Modulation of growth hormone action by sex steroids, 65 Clin. Endocrinol. 413, 414 (2006).

32. The neurological and psychological changes occurring in puberty are less well understood than are the physiological changes. Men and women have distinct neurological features that may account for some of the psychological differences between the sexes, though the extent to which neurological differences account for psychological differences, and the extent to which neurological differences are caused by biological factors like hormones and genes (as opposed to environmental factors like social conditioning), are all matters of debate.

33. Scientists distinguish between two types of effects hormones can have on the brain: organizational effects and activational effects. Organizational effects are the ways in which hormones cause highly stable changes in the basic architecture of different brain regions. Activational effects are the more immediate and temporary effects of hormones on the brain's activity. During puberty, androgens and estrogens primarily have activating effects, but long before then they have organizational effects in the brains of developing infants and fetuses.[26]

34. In sum: Puberty involves a myriad of complex, related, and overlapping physical processes, occurring at various points and lasting for various durations. During this period of life, adrenarche and changes in the secretion of growth hor-

[26] M. M. Herting et al., Puberty and structural brain development in humans, 44 Frontiers in Neuroendocrinol. 122 (2017); J. Hornung et al., Sex hormones and human brain function, 195 Handb. Clin. Neurol. 175 (2020).

mone contribute to the child's growth and development. With gonadarche, the maturation of sex organs begins and with normal maturation will lead to the emergence of reproductive capacity, as well as the development of the other biological characteristics that distinguish males and females.

PEDIATRIC ENDOCRINE DISORDERS AND TREATMENTS

35. The field of endocrinology is directed toward the care of hormone-related diseases. Pediatric endocrine diseases include disorders of glucose regulation (hypoglycemia and diabetes mellitus), disorders of thyroid function (hyper and hypothyroidism), disorders of growth (e.g., short stature, acromegaly, obesity, and poor weight gain), disorders of sexual development and function (e.g., genital ambiguity, precocious and delayed puberty, hypogonadism, polycystic ovarian syndrome), disorders of adrenal function (e.g., adrenal insufficiency and Cushing's syndrome), disorders of pituitary function, lipid disorders, and disorders of bone and mineral metabolism. For all of these conditions, there are objective physical and biochemical criteria for diagnosis and treatment with well-established normal reference ranges for hormones and metabolites.

I. Using GnRH Analogues — "Puberty Blockers" — to Treat Precocious Puberty and Other Conditions

36. Hormone interventions to suppress puberty were not developed for the purpose of treating children with gender dysphoria. Rather, they were first used as

a way to normalize puberty for children who undergo puberty too early, a condition known as "precocious puberty."

37. For females, precocious puberty is defined by the onset of puberty before age 8, while for males it is defined as the onset of puberty before age 9.[27] Premature thelarche (the appearance of breast development) is usually the first clinical sign of precocious puberty in girls. For males, precocious puberty is marked by premature testicular enlargement.[28] In addition to the psychological and social consequences that a child might be expected to suffer, precocious puberty can also lead to reduced adult height, since the early onset of puberty interferes with later bone growth.[29]

38. Precocious puberty is divided into two types, central precocious puberty (sometimes labeled "true precocious puberty") and peripheral precocious puberty (sometimes labeled "precocious pseudopuberty").[30] Central precocious puberty is caused by the early activation of the gonadal hormone pathway by GnRH,

[27] K. O. Klein, Precocious Puberty: Who Has It? Who Should Be Treated?, 84 J. Clin. Endocrinol. & Metabol. 411 (1999). See also F. M. Biro et al., Onset of Breast Development in a Longitudinal Cohort, 132 Pediatrics 1019 (2013); C.-J. Partsch et al., Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens, 7 Human Reproduction Update 292, 293 (2001).
[28] A. Parent et al., The Timing of Normal Puberty and the Age Limits of Sexual Precocity: Variations around the World, Secular Trends, and Changes after Migration, 24 Endocrine Revs. 675 (2011).
[29] J.-C. Carel et al., Precocious puberty and statural growth, 10 Human Reproduction Update 135 (2004).
[30] C.-J. Partsch et al., Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens, at 294-95.

and is amenable to treatment by physicians. Peripheral precocious puberty, which is caused by secretion of sex hormones by the gonads or adrenal glands independent of signals from the pituitary gland, is less amenable to treatment. Effects of androgen or estrogen hypersecretion can be reduced by administration of drugs that block the activity of the sex hormone receptors. If a tumor is causing the disorder, surgical removal may be necessary.

39. Precocious puberty is rare, especially in boys. A recent Spanish study of central precocious puberty estimated the overall prevalence to be 19 in 100,000 (37 in 100,000 girls affected, and 0.46 in 100,000 boys).[31] A Danish study of precocious puberty (not limited to central precocious puberty) found the prevalence to be between 20 to 23 per 10,000 in girls and less than 5 in 10,000 in boys.[32]

40. To diagnose central precocious puberty, hormones from the pituitary gland, LH and FSH, are objectively measured. This can sometimes be done by measurement of baseline levels[33] but often requires assessment after transient stimulation with GnRH. As discussed, these are two hormones that are made in the pi-

[31] L. Soriano-Guillén et al., Central Precocious Puberty in Children Living in Spain: Incidence, Prevalence, and Influence of Adoption and Immigration, 95 J. Clin. Endocrinol. & Metabol., 4305, 4307 (2011). In some cases, peripheral precocious puberty is caused by an underlying condition, such as a tumor, that can be treated.

[32] G. Teilmann et al., Prevalence and Incidence of Precocious Pubertal Development in Denmark: An Epidemiologic Study Based on National Registries, 116 Pedriatics 1323 (2005).

[33] S. Heo et al., Basal Serum Luteinizing Hormone Value as the Screening Biomarker in Female Central Precocious Puberty, 24 Annals of Pediatr. Endocrinol. & Metabol., 164, 164-71 (2019).

tuitary gland that signal to the gonads. In males, they lead to production of testosterone. In females, they lead to the production of estrogen. LH and FSH signaling are essential for normal sperm production and ovarian maturation in males and females, respectively.

41. Also subject to objective measurement when diagnosing and treating central precocious puberty are sex steroid hormones, either testosterone or estrogen, and bone growth.

42. Treatment for precocious puberty is somewhat counterintuitive. Rather than stopping the production of GnRH, physicians actually provide patients more constant levels of synthetic GnRH (called GnRH analogues or GnRH agonists).[34] As discussed above, when produced endogenously (that is, by the body naturally), GnRH stimulates the pituitary gland to release gonad-stimulating hormones (gonadotropins, LH and FSH). When added exogenously, the additional GnRH "desensitizes" the pituitary, leading to a decrease in the secretion of gonadotropins, which in turn leads to the decreased maturation of and secretion of sex hormones by the gonads (ovaries and testes). The intent and effect of giving puberty blockers is identical when it is given to a male as when it is given to a female in this context: suppressing

[34] W. F. Crowley, Jr. et al., Therapeutic use of pituitary desensitization with a long-acting LHRH agonist: a potential new treatment for idiopathic precocious puberty, 52 J. Clin. Endocrinol. & Metabol., 370, 370-72 (1981) (LHRH refers to "luteinizing hormone releasing hormone," another term for GnRH.).

the secretion of gonadotropin hormones. Even the dosing is the same for males and females, and depends on the person's weight.

43. The first publication describing the use of GnRH analogues in children for precocious puberty appeared in 1981.[35] In the time since GnRH analogues were first proposed, they have become fairly well accepted as a treatment of precocious puberty, with one prominent GnRH analogue, Lupron, approved for that use by the FDA in 1993.[36] However, there remain some questions concerning the effectiveness of treatment with GnRH analogues. A 2009 consensus statement of pediatric endocrinologists concluded that GnRH analogues are an effective way to improve the height of girls with onset of puberty at less than 6 years of age, and also recommended the treatment be considered for boys with onset of precocious puberty who have compromised height potential.[37] Regarding the negative psychological and so-

[35] *Id.*
[36] "Full Prescribing Information" for Lupron Depot-Ped, FDA.gov (undated), https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020263s036lbl.pdf (last visited April 6, 2023).
[37] J.-C. Carel et al., Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children, 123 Pediatrics e752, e753 (2009).

cial outcomes associated with precocious puberty, the authors found that the available data were unconvincing, and that additional studies are needed.[38] Puberty blockers have recently been recognized to carry a risk of increased brain pressure that can adversely affect vision and cause severe headaches.[39]

44. When used to treat precocious puberty, the process of desensitization of the pituitary gland by synthetic GnRH is not permanent. After a patient stops taking the GnRH analogues, the pituitary will resume its normal response to the pulsatile secretion of GnRH by the hypothalamus, as evidenced by the fact that children treated for precocious puberty using GnRH analogues will resume normal pubertal development, usually about a year after they withdraw from treatment.[40]

45. The goal of treating precocious puberty is to allow the child to have pubertal development enter the normal quiescence that is present at that age. This treatment helps to preserve their final adult height, by slowing the rate of bone age advancement. The goal is *not* to delay puberty beyond other children, as delaying too long can lead to adverse effects, including reduced bone marrow density, as discussed below.

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[38] *Id.*

[39] Risk of pseudotumor cerebri added to labeling for gonadotropin-releasing hormone agonists, AAP News, July 1, 2022, https://publications.aap.org/aapnews/news/20636/Risk-of-pseudotumor-cerebri-added-to-labeling-for?autologincheck=redirected (last visited April 7, 2023).

[40] M. M. Fisher et al., Resumption of Puberty in Girls and Boys Following Removal of the Histrelin Implant, 164 J. Pediatrics 912, 912-16 (2014).

46. In addition to being prescribed for children with precocious puberty, GnRH analogues have also been used in adults for a variety of indications, including hormone-sensitive tumors.[41] GnRH analogues have also been given to post-pubertal adolescents undergoing chemotherapy with drugs that can have toxic effects on the gonads.[42]

II. Using Sex Steroids Such as Testosterone and Estrogen to Treat Disorders of Normal Gonadal Function

47. Sex steroids such as testosterone and estrogen are frequently used in the treatment of disorders of normal gonadal function. This includes hypogonadotropic hypogonadism, primary gonadal failure, and delayed puberty.[43] In each of these conditions, there are objective laboratory tests that are used to diagnose these conditions and monitor response to treatment. Deficiency of sex steroids has bodily effects that extend beyond sexual function.[44] This includes significant effect on bone density, lean body mass, metabolism, immunity, and neural function.

[41] See P. Kumar et al., Gonadotropin-releasing hormone analogs: Understanding advantages and limitations, 7 J. Human Reproductive Scis. 170 (2014).
[42] M. Meli et al., Triptorelin for Fertility Preservation in Adolescents Treated With Chemotherapy for Cancer, 40 J. Pediatr. Hematol./Oncol. 269 (2018).
[43] P. Kumar et al., Male hypogonadism: Symptoms and treatment, 1 J. Advanced Pharmaceutical Technology & Research 297 (2010); K. Voutsadaki et al., Hypogonadism in adolescent girls: treatment and long-term effects, 93 Acta Biomedica Atenei Parmensis e2022317 *1 (2022).
[44] M. Alemany, The Roles of Androgens in Humans: Biology, Metabolic Regulation and Health. 23 Int'l. J. Molecular Scis. 11952 (2022); S. Patel et al., Estrogen: The necessary evil for human health, and ways to tame it, 102 Biomed. & Pharmacother. 403 (2018).

48. There are major and highly significant differences between male and female responses to sex hormones.[45] Giving estrogen to a biological male is not equivalent to giving the same hormone to a biological female. Likewise, giving testosterone to a biological female is not equivalent to giving the same hormone to a biological male.[46] Differences are not limited to pharmacokinetic effect (i.e., how drugs are absorbed, distributed throughout the body, and metabolized) but are present even at the cellular level.[47] Sex steroids act by altering the expression of the genetic information present in all nucleated cells of the body. Epigenetic differences (i.e., chemical changes to DNA structure) result in sex-differential expression of over 6,500 genes in the body.[48] Consequences of a failure to recognize these differences can result in drug overdose, lack of treatment response, or serious side effects.

49. Several conditions in male minors may indicate a need for endocrinologic treatment with testosterone. For instance, primary hypogonadism from gonadal failure is caused by damage or impaired function of the male testes. Secondary

[45] See C. Madla et al., Let's talk about sex: Differences in drug therapy in males and females, 175 Advanced Drug Delivery Revs. 113804 (2021).
[46] See O. P. Soldin et al., Sex Differences in Pharmacokinetics and Pharmacodynamics, 48 Clin. Pharmacokinetics 143 (2009); S. Pogun et al., Sex Differences in Drug Effects, in Encyclopedia of Psychopharmacology, 1210, 1210-16 (I. P. Stolerman, ed., 2010).
[47] See, e.g., C. J. Walker et al., Matters of the heart: Cellular sex differences, 160 J. Molecular and Cellular Cardiol. 42 (2021).
[48] M. Gershoni et al., The landscape of sex-differential transcriptome and its consequent selection in human adults, 15 BMC Biol. 7 (2017).

hypogonadism is caused by abnormalities in pituitary structure or function. Hypogonadism can be objectively diagnosed by measurement of testosterone (or its derivatives) and gonadotropin (LH and FSH) levels. When used for the treatment of affected males with hypogonadism, testosterone is administered to achieve levels that are normal for males of the patient's age. For young adult Tanner Stage 5 males, normal testosterone levels range from 300-900 ng/dL.[49] Achievement of appropriate testosterone levels requires careful monitoring, as excess levels can have serious adverse effects, including elevations of red blood cell counts, changes in blood pressure, and brain changes.[50]

50. Testosterone may also be used in males to treat delayed puberty. To treat the condition of constitutional delay (where the person has means to progress through puberty, but onset was delayed), the male would normally be given low doses of testosterone for 3-4 months to "prime the pump" for normal puberty. Assessment of this condition includes measuring levels of LH, FSH, and testosterone, as well as observation of testicular size. Once puberty has been initiated and is pro-

[49] T. G. Travison et al., Harmonized Reference Ranges for Circulating Testosterone Levels in Men of Four Cohort Studies in the United States and Europe, 102 J. Clin. Endocrinol. & Metabol., 1161 (2017).

[50] S. J. Ohlander et al., Erythrocytosis Following Testosterone Therapy, 6 Sexual Medicine Revs. 77 (2018); T. Kienitz et al., Testosterone and Blood Pressure Regulation, 31 Kidney and Blood Press. Rsch. 71 (2008); M. Scarth et al., Androgen abuse and the brain, 28 Curr. Op. in Endocrinol., Diabetes & Obes. 604 (2021).

gressing, there is no need to administer ongoing testosterone therapy. Normal gonadotropin (LH and FSH) signaling from the pituitary gland will allow continued maturation of the testes, leading to reproductive capacity.

51. Continuing to give external testosterone to a male in normal puberty would suppress the normal function of the testes and can lead to infertility — a result contrary to the goal of endocrinology, which is to restore health. Thus, for instance, a male adolescent undergoing normal puberty who simply desired increased lean body mass (i.e., higher muscle mass) should not normally be given testosterone for that purpose, both because it is considered medically unnecessary and because of the adverse effects of extra testosterone. Among other reasons, these effects explain why testosterone is a controlled substance.

52. Outside the context of gender dysphoria, testosterone is not an indicated treatment for a female child or adolescent. Testosterone, or any androgen, would lead to virilization, which can come with serious adverse effects. This includes impaired fertility, alopecia (hair loss), disfiguring acne, and metabolic changes that increase risk of heart disease and diabetes.[51]

53. Estrogen can be given to young females to treat the same conditions testosterone treats in young males: constitutional delay and hypogonadism, either

[51] R. Yang et al., Effects of hyperandrogenism on metabolic abnormalities in patients with polycystic ovary syndrome: a meta-analysis, 14 Reproductive Biol. and Endocrinol. 67 (2016).

primary or secondary. Primary hypogonadism is caused by a defect in the presence or function of the ovaries. Secondary hypogonadism is caused by a defect in the structure or function of the pituitary gland. A female can experience premature ovarian insufficiency where the ovaries become inactive over time, both genetically and through environmental incidents. To diagnose these conditions, hormone levels can be objectively measured. This includes LH, FSH, estradiol, and other levels. (Estradiol is a form of estrogen, and generally the main hormone followed and measured in female endocrinologic practice.) Female estrogen levels will vary throughout the menstrual cycle but are normally 30-400 pg/mL.[52] The physical response to the intervention can also be measured.

54. Estrogen treatments carry risks, including stroke, elevated blood pressure, and changes to bone development. Males are not generally prescribed estrogen (again, outside the context of gender dysphoria), and there is concern that the risks of estrogen are even higher in males.

GENDER DYSPHORIA AND ENDOCRINE TREATMENTS

55. In contrast to the conditions discussed above, gender dysphoria is not an endocrine disorder. Instead, it is a diagnostic term for "the distress that may accompany the incongruence between one's experienced or expressed gender and

[52] S. Verdonk et al., Estradiol reference intervals in women during the menstrual cycle, postmenopausal women and men using an LC-MS/MS method, 495 Clinica Chimica Acta 198, 198-204 (2019).

one's" biological sex.[53] Gender dysphoria is associated with high rates of comorbidity, including suicidal ideation, depression, anxiety, poverty, homelessness, eating disorders, and HIV infection.[54] Gender dysphoria as a psychiatric disorder should be distinguished from identifying as transgender or transsexual. As noted, people who identify as transgender "transiently or persistently identify with a gender different from their natal gender." In this definition, "natal gender" refers to sex. Transsexual has an even more specific meaning; it "denotes an individual who seeks, or has undergone, a social transition from male to female or female to male, which in many, but not all, cases also involves a somatic transition by cross-sex hormone treatment and genital surgery."[55]

56. Some practitioners promote a so-called "gender affirming" approach to treating gender dysphoria, which involves affirming the child's present gender identity. This affirmation may have social, medical, legal, and behavioral dimensions. Typically, this "affirming" approach encourages children to embrace transgender identity with social transitioning followed by puberty blockade and hormonal therapy (cross-sex hormones), and potential surgical interventions.[56] This approach,

[53] DSM-5, at 451.
[54] M. D. Connolly et al., The Mental Health of Transgender Youth: Advances in Understanding, 59 J. Adolesc. Health 489 (2016); F. Pinna et al., Mental health in transgender individuals: a systematic review, 34 Int'l Rev. of Psychiatry 292 (2022).
[55] DSM-5, at 451.
[56] See A. Walch et al., Proper Care of Transgender and Gender Diverse Persons in the Setting of Proposed Discrimination: A Policy Perspective, 106 J. Clin. Endocrinol. & Metabol. 305 (2021).

specifically in the context of using puberty blockers and cross-sex hormones, is considered below.

57. Before analyzing gender affirmative medical interventions, it is important to understand that underlying biology is not changed by altering bodily features to appear as the opposite sex, and such alterations do not change disease vulnerabilities and drug responses associated with genetically defined sex.[57] Despite the increasing ability of hormones and various surgical procedures to reconfigure some male bodies to visually pass as female, or vice versa, the biology of the person remains as defined by genetic makeup, normatively by his (XY) or her (XX) chromosomes, including cellular, anatomic, and physiologic characteristics and the particular disease vulnerabilities associated with that chromosomally-defined sex.[58] For instance, the XX (genetically female) individual who takes testosterone to stimulate certain male secondary sex characteristics will nevertheless remain unable to produce sperm and father children. It is possible for some adolescents and adults to

[57] See Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016 Oct;16(10):626-38 and Karlsson Lind L, et al. Sex differences in drugs: the development of a comprehensive knowledge base to improve gender awareness prescribing. Biol Sex Differ. 2017 Oct 24;8(1):32.

[58] See Exploring the biological contributions to human health: does sex matter?, (Institute of Medicine (U.S.), T. M. Wizemann, & M. L. Pardue eds., 2001) (hardcover edition); Exploring the Biological Contributions to Human Health: Does Sex Matter?, (2001), http://www.nap.edu/catalog/10028 (last visited Apr 8, 2023) (electronic editions).

pass unnoticed as the opposite gender that they aspire to be — but with limitations, costs, and risks.[59] And their underlying biology does not change.

I. Puberty Blockers

58. Only in the 1990s did GnRH analogues begin being used to suppress puberty in children who identify as the opposite sex. In 1998, Peggy Cohen-Kettenis and Stephanie van Goozen, psychologists at a Dutch gender clinic, described the case of a 13-year-old female gender-dysphoria patient, on whom a GnRH analogue was used to suppress puberty before the patient received a definitive diagnosis of gender identity disorder at age 16. At age 18, the patient underwent sex-reassignment surgery.[60]

59. The clinic's scientists developed an influential protocol, often referred to as the "Dutch protocol," which involved puberty suppression followed by cross-sex hormones and potential surgical interventions.[61] In many clinics that adhere to the gender affirmation model, the ages for initiating sex-discordant, gender-affirming, sex-steroid hormones has deviated substantially from the original Dutch

[59] See S. B. Levine, Informed Consent for Transgendered Patients, 45 J. Sex & Marital Therapy, 218 at *6 (2018) ("Informed Consent"); S. B. Levine, Reflections on the Legal Battles Over Prisoners with Gender Dysphoria, 44 J. Am. Acad. Psychiatry & L. 236, 238 (2016) ("Reflections on Legal Battles").

[60] P. T. Cohen-Kettenis et al., Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent, 7 Eur. Child & Adolesc. Psychiatry 246 (1998). See also P, T. Cohen-Kettenis et al., Treatment of Adolescents With Gender Dysphoria in the Netherlands, 20 Child and Adolesc. Psychiatric Clinics of N. Am. 689 (2011).

[61] M. Biggs, The Dutch Protocol for Juvenile Transsexuals: Origins and Evidence, J. Sex & Marital Therapy, 1 (Sept.19, 2022).

protocol. In current protocols puberty blockers (GnRH analogs) are initiated as soon as puberty begins (Tanner Stage 2), which can occur as early as 8 years in females and 9 years in males. While in the Dutch protocol, cross-sex hormones started at 16 years, the Standards of Care for the Health of Transgender and Gender Diverse People, Version 8 (SOC-8), the latest guidelines published by the World Professional Association for Transgender Health (WPATH), made no recommendations on specific ages for initiation of gender-affirming medical interventions, stating that decisions need to be made on an individual basis with the possibility of there being compelling reasons to start interventions earlier.[62] Due to the suppressive effect of exogenous sex-steroids on gonadal function, GnRH analogs are often stopped after gender-affirming hormone administration has been titrated to maximal doses required to achieve the desired change in secondary sex characteristics.

60. These scientists, along with others, have claimed that puberty suppression is "fully reversible."[63] On this view, puberty suppression "give[s] adolescents, together with the attending health professional, more time to explore their gender

[62] E. Coleman et al., Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, 23 Int'l. J. Transgender Health, 51-5258, 556-66, S1, S65-66 (Sept. 6, 2022) ("SOC-8").
[63] H. A. Delemarre-van de Waal et al., Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects, 155 Eur. J. of Endocrinol., S131, S133 (Nov. 1, 2006).

identity, without the distress of the developing secondary sex characteristics. The precision of the diagnosis, it is claimed, may thus be improved."[64]

61. Given their potential importance in the lives of the affected children, claims about reversibility require careful examination. In developmental biology, it makes little sense to describe anything as "reversible." If a child does not develop certain characteristics at age 12 because of a medical intervention, then his or her developing those characteristics at age 18 is not a "reversal," since the sequence of development has already been disrupted. This is especially important since there is a complex relationship between physiological and psychosocial development during adolescence. A more relevant question is whether the physiological and psychosocial development that occurs during puberty can resume in something resembling a normal way after puberty-suppressing treatments are withdrawn. In children with precocious puberty, this does appear to be the case. Puberty-suppressing hormones are typically withdrawn around the average age for the normal onset of gonadarche, at about age 12, and normal hormone levels and pubertal development gradually resume. For one common method of treating precocious puberty, girls reached menarche approximately a year after their hormone treatments ended, at an average age

[64] P. T. Cohen-Kettenis et al., The Treatment of Adolescent Transsexuals: Changing Insights, 5 J. Sexual Med. 1892, 1894 (2008).

of approximately 13, essentially the same average age as the general population.[65] The evidence for the safety and efficacy of puberty suppression in boys is less robust, chiefly since precocious puberty is much rarer in boys. Although the risks are speculative and based on limited evidence, boys who undergo puberty suppression may be at greater risk for the development of testicular microcalcifications, which may be associated with an increased risk of testicular cancer, and puberty suppression in boys may also be associated with obesity.[66]

62. Unlike children affected by precocious puberty, adolescents with gender dysphoria do not have any physiological disorders of puberty that are being corrected by the puberty-suppressing drugs. The fact that children with suppressed precocious puberty between ages 8 and 12 resume puberty at age 13 does not mean that adolescents suffering from gender dysphoria whose puberty is suppressed beginning at age 12 will simply resume normal pubertal development later if they choose to withdraw from the puberty-suppressing treatment and choose not to undergo other sex-reassignment procedures. Interrupting puberty in this manner may have significant effects on final stature and bone density.[67]

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[65] M. M. Fisher et al., Resumption of Puberty in Girls and Boys Following Removal of the Histrelin Implant, 164 J. Pediatrics 912, 912-16 (2014).
[66] S. Bertelloni, Treatment of central precocious puberty by GnRH analogs: long-term outcome in men, 10 Asian J. Androl. 525, 531 (2008).
[67] T. Joseph et al., The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort, 32 J. Pediatric Endocrinol. and Metabol. 1077, 1077-81 (2019); D, Klink et al., Bone Mass in Young Adulthood Following

63. After an extended period of pubertal suppression one cannot "turn back the clock" and reverse changes in the normal coordinated pattern of adolescent psychological development and puberty.[68] Once puberty is blocked, even if eventually unblocked (and assuming signaling from the pituitary gland resumes), the person cannot "buy back" the time when the physical process of puberty has been disrupted at the time when it would normally occur with complementary psychological processes in that stage in the person's life.

64. A possible effect of blocking normally timed puberty is alteration of normal adolescent brain maturation.[69]

65. In addition to the reasons to suspect that puberty suppression may have side effects on physiological, psychological, and brain development, the evidence that something like normal puberty will resume for these patients after puberty-suppressing drugs are removed is very weak. Data obtained from the treatment of precocious puberty cannot be assumed to apply equally to the disruption of puberty that begins after 8 years of age in females and after 9 years of age in males.

Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria, 100 J. Clin. Endocrinol. & Metabol., E270-E275 (2015).

[68] See P. W. Hruz et al., Growing Pains, 52 The New Atlantis: A Journal of Technology and Society, 3 (Spring 2017). See also N. Vijayakumar et al., Puberty and the human brain: Insights into adolescent development, 92 Neurosci. & Biobehav. Revs 417 (2018); S. Choudhury, Culturing the adolescent brain: what can neuroscience learn from anthropology?, 5 Social Cognitive and Affective Neurosci. 159 (2010).

[69] See M. Arain et al., Maturation of the adolescent brain, 9 Neuropsychiatric Disease and Treatment, 449 (2013).

66. In addressing the concern of puberty blockers on bone density, it is important to recognize that bone density is normally increasing during the teenage years. Observing an increase in bone density measurement does not indicate lack of adverse effect.[70] The relevant parameter is the bone density in relation to mean bone density in age and size matched controls. This is generally assessed as a "z-score." In the study by Klink[71] and it was observed that with blockade of normally timed puberty, there was a failure to regain pre-treatment z-scores for bone density even after introduction of cross-sex hormones. This supports the concern that interruption of normally timed puberty adversely affects bone density.

67. In Dr. Shumer's declaration (page 18, ¶ 69) he correctly acknowledges that it is necessary "to complete puberty to produce viable eggs or sperm." However, he fails to present the existing evidence that nearly all patients who are placed on puberty blockers will proceed to cross-sex hormones.[72] As discussed next, it is this later drug exposure that is of concern for irreversible sterility. There are no existing data to demonstrate that the exposure of immature gonads to sex-hormones corresponding to the opposite sex is "safe and reversible." The study of Caanen, et al.,

[70] L. K. Bachrach, Acquisition of optimal bone mass in childhood and adolescence, 12 Trends in Endocrinol. & Metabol. 22 (2001).
[71] Klink et al., Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria, 100 J. Clin. Endocrinol. & Metabol., E270-E275 (2015)
[72] M. A. T. C. van der Loos et al. (2022), Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence, 6 Lancet Child & Adolesc. Health, at 869-75.

cited by Dr. Shumer to support this assertion,[73] assesses ovarian morphology not fertility. Most if not all of the subjects were exposed to testosterone after menarche. Table 2 in this paper lists the average age of menarche as 12 years. The median age of testosterone initiation as 20.5 years and the median duration of testosterone treatment was 29.5 months. The authors of this paper do not state when GnRH analogs were started. Only 1 of the 54 transgender subjects had a pregnancy and none delivered a child. For comparison, 51.7% of the control group without testosterone exposure had pregnancy and 37.5% delivered a child. The concern for irreversible effects on fertility is the basis for recommendations to cryopreserve sperm or eggs prior to initiation of this intervention.[74]

II. Cross-Sex Hormones

68. Rather than resuming biologically normal puberty, adolescents treated on the "affirming" model overwhelmingly go from suppressed puberty to medically conditioned cross-sex puberty, when they are administered cross-sex hormones.[75]

[73] Caanen MR, et al. (2017). Effects of long-term exogenous testosterone administration on ovarian
morphology, determined by transvaginal (3D) ultrasound in female-to-male transsexuals. Hum Reprod. 32(7):1457-1464

[74] P, J. Cheng et al., Fertility concerns of the transgender patient, 8 Translational Androl. and Urol. 209 (2019).

[75] M. A. T. C. van der Loos et al. (2022), Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence, 6 Lancet Child & Adolesc. Health, at 869-75.

Specifically, exogenous estrogen is administered to biological men to induce gynecomastia (i.e., the enlargement of breast tissues), and testosterone is administered to biological women to induce virilization (i.e., the development of facial hair and other desired male features) and to interfere with normal ovarian function.

69. Along with (and often before) estrogen is administered to biological males in this treatment, spironolactone may be used as an androgen blocker. Spironolactone is primarily used for the treatment of blood pressure and heart failure. It is a mineralocorticoid antagonist, meaning that it blocks the function of proteins in the kidney that regulate salt retention. But it also has effects in blocking the action of androgens. As discussed, androgens are masculinizing hormones that lead to virilization. Testosterone is a prime androgen, but other androgens are also made in the gonads and adrenal gland. Spironolactone is sometimes used in the treatment of polycystic ovarian syndrome, in which females will undergo virilization due to excess androgen production in the ovaries. This syndrome can have adverse effects on fertility, metabolic health, and cardiovascular health.[76] The diagnosis of polycystic ovarian syndrome is a clinical diagnosis based upon the physical evidence of virilization or androgen effects, insulin resistance, and irregular periods. There are objective biological measures to assess those androgen levels, most notably elevated

[76] M. H. Hunter et al., Polycystic Ovary Syndrome: It's Not Just Infertility, 62 Am. Fam. Physician 1079, 1079-88 (2000).

free testosterone levels. And there are objective measures of dysregulation of relevant signals from the pituitary gland, the LH and the FSH, to complement the clinical diagnosis by looking at the degree of virilization that is present in the patient.

70. Spironolactone would not be prescribed to male patients for an endocrinologic purpose related to androgen production. Once again, this reflects a fundamental biological difference between males and females. Though spironolactone can be used to regulate the levels of potassium and sodium in the body, such treatment would be based on objective markers of those levels.

71. Likewise, the administration of the sex steroid hormones differ by the sex of the individual. It is not identical to give testosterone to a male as it is to give it to a female, nor is it the same treatment to give estrogen to a male versus female. This difference has an established scientific basis. The differences between males and females occurs in every nucleated cell of the body, for males and females have different genetic programming. This is a process known as epigenetics, meaning that there are modifications of the DNA itself that alter the expression of genes when exposed to the same stimulus. As noted above, there are over 6,000 sex-differentially expressed genes. So, if one gives testosterone to a male, the physiologic effects

of that treatment, even in the measurement at which genes are turned on and turned off, will be different than if one gives testosterone to a female.[77]

72. In congenital or acquired conditions where there is a defect in the ability to produce endogenous sex-steroid hormones, the goal of administering testosterone or estrogen is to restore the body to its natural state had the defect not been present. For example, females with Turner syndrome have premature ovarian failure and are therefore given estrogen to preserve bone health and allow normal pubertal maturation. Males with Klinefelter syndrome have primary hypogonadism and are therefore given testosterone to achieve normal lean body mass, bone density, hematocrit, and other androgen mediated bodily changes. Importantly, sex-steroid hormone doses are adjusted to maintain levels within the normal range for the sex of that individual.

73. While the normal range for testosterone levels in a male adolescent who has completed puberty is 300-900 ng/dL, testosterone levels for a female adolescent are 15-70 ng/dL. Testosterone levels can be elevated in females with pathologic conditions such as polycystic ovarian syndrome, but levels generally are less than 150 ng/dL. Levels above 200 ng/dL would generally necessitate evaluation for an adrenal or ovarian tumor.

[77] M. Gershoni et al., The landscape of sex-differential transcriptome and its consequent selection in human adults, 15 BMC Biol. 7 (2017)

74. When a patient with gender dysphoria is placed on cross-sex hormones, per the Dutch protocol, puberty-suppressing GnRH analogues continue to be administered until exogenous administration of cross-sex hormones (i.e., sex hormones normally produced by the gonads of the opposite sex) leads to sufficient suppression of endogenous sex hormone production, or the gonads are surgically removed. With pubertal blockade, sex hormones that are normally secreted by the maturing gonads are not produced. This means that adolescents undergoing cross-sex hormone treatment circumvent the most fundamental form of sexual maturation — the maturation of their reproductive organs.

75. For males who are being medically transitioned, exogenously administered estrogen will suppress testosterone production through feedback inhibition of pituitary LH and FSH secretion. Without pubertal blockade, this reduction of endogenous testosterone production is usually not sufficient to fully prevent virilization, and it is therefore necessary to add anti-androgenic medications such as spironolactone. For females being medically transitioned, exogenously administered testosterone will usually result in the cessation of menses and lead to the expected effect of virilization.

76. Patients undergoing gender affirming surgery discontinue GnRH treatment after having their gonads removed, since the secretion of sex hormones that the treatment is ultimately intended to prevent will no longer be possible. These patients

are then sterile, as loss or alteration of primary sexual organs leads directly to impairment of reproductive potential.

77. Although the long-term effect of exposing immature gonads to cross-sex hormones is currently unknown, it is generally accepted, even by advocates of transgender hormone therapy, that hormonal treatment impairs fertility, which may be irreversible.[78] Specifically, estrogen administration to males who identify as women results in impaired spermatogenesis and an absence of Leydig cells in the testis.[79] Exogenous testosterone administration to females who identify as men causes ovarian stromal hyperplasia and follicular atresia.[80] Recognition of these consequences is the basis for the development of new areas of medical practice where there is an attempt to restore fertility that has been intentionally destroyed.[81]

78. Gametes (sperm and ova) require natural puberty to mature to the point that they are viable for reproduction.[82] While it is expected that the exposure of

[78] See L. Nahata et al., Low Fertility Preservation Utilization Among Transgender Youth, 61 J. Adolesc. Health 40 (2017).
[79] C. Schulze, Response of the human testis to long-term estrogen treatment: Morphology of Sertoli cells, Leydig cells and spermatogonial stem cells, 251 Cell and Tissue Rsch. 31 (1988).
[80] T. D. Pache et al., Ovarian morphology in long-term androgen-treated female to male transsexuals. A human model for the study of polycystic ovarian syndrome?, 19 Histopathol. 445 (1991); K. Ikeda et al., Excessive androgen exposure in female-to-male transsexual persons of reproductive age induces hyperplasia of the ovarian cortex and stroma but not polycystic ovary morphology 28 Human Reproduction 453 (2013).
[81] See, e.g., A. J. Ainsworth et al., Fertility Preservation for Transgender Individuals: A Review, 95 Mayo Clinic Proceedings 784, 784-92 (2020).
[82] H. E. Kuhn et al., The Onset of Sperm Production in Pubertal Boys: Relationship to Gonadotropin Excretion, 143 Am. J. Diseases in Children 190 (1989).

immature gonads to cross-sex hormones will lead to infertility, whether affected individuals have permanent sterility has not been established. Much of the uncertainty arises from the novelty of this intervention and the lack of long term follow up. There are limited reports of successful pregnancies after cross-sex hormones, but all of the subjects started gender-affirming hormones as adults after completing puberty.[83] While Dr. Shumer's report in this case implies that it is possible for an adult patient who was previously treated with GnRHa followed by hormone therapy to achieve fertility by withdrawing hormones (pages 18-19), he does not provide any published data to support this assertion. I am not aware of any reports that show this for children who were exposed to puberty blockers before completing puberty followed by cross-sex hormones.

79. There are many other known risks to puberty suppression followed by cross-sex hormones beyond fertility concerns. As noted, emerging data show that treated patients have lower bone density, which may lead to increased fracture risk later in life.[84] Other potential adverse effects include disfiguring acne, high blood pressure, weight gain, abnormal glucose tolerance, breast cancer, liver disease,

[83] I. de Nie et al., Successful restoration of spermatogenesis following gender-affirming hormone therapy in transgender women, 4 Cell Reports Med. 100858 (2023).
[84] See D. Klink et al. (2015), Bone Mass in Young Adulthood, 100 J. Clin. Endocrinol. & Metabol., at E270-E275.

thrombosis, and cardiovascular disease.[85] In addition, non-physiological levels of estrogen in males has been shown to increase the risk of thromboembolic stroke above the incidence observed in females.[86]

80. Dr. Shumer and other advocates of the gender affirmation approach to gender dysphoria often make misleading or erroneous statements about the potential or known adverse effects of interrupting normally timed puberty with GnRH analogues and the administration of "gender-affirming" sex-steroid hormones. This includes appeal to data on the safety of using these drugs in treating precocious puberty, where the effect of the intervention is to restore the patient to the normal phase of quiescence of the pituitary-gonadal axis (Shumer declaration ¶ 69). Further assertions that such treatments are the same as those used to treat conditions that are associated with infertility, such as Turner syndrome and Klinefelter syndrome (Shumer declaration ¶ 74), ignore the striking differences in both physiological attributes and goal of intervention. Some potential adverse effects can only be ascertained with directed testing that goes beyond what is normally performed as

[85] See L. J. Seal, A review of the physical and metabolic effects of cross-sex hormonal therapy in the treatment of gender dysphoria, 53 Annals Clin. Biochem. 10 (2016); K. Banks et al., Blood Pressure Effects of Gender-Affirming Hormone Therapy in Transgender and Gender-Diverse Adults, 77 Hypertension 2066, 2066-74 (2021); D. Getahun et al., Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study, 169 Annals of Internal Med. 205 (2018); S. Maraka et al., Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A Systematic Review and Meta-Analysis, 102 J. Clin. Endocrinol. & Metabol., 3914, 3914-23 (2017).

[86] See, e.g. D. Getahun et al. (2018), Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons, 169 Annals of Internal Med., at 205, *6-*8.

screening tests done in medical clinics. Cancer and cardiovascular and metabolic risks often take decades to manifest. The failure to observe patients with myocardial infarction (heart attack), thromboembolic events (stroke), or cancer in adolescent patients exposed to testosterone or estrogen at levels at or exceeding those observed in known disease states (e.g., polycystic ovarian syndrome or hormone-secreting tumors) does not mitigate concerns with these interventions in youth who experience sex-discordant gender identity.

ENDOCRINE SOCIETY GUIDELINES

81. A reasonable understanding of relative risk versus benefit for medical products or procedures is a fundamental obligation in providing appropriate clinical care. This is the bedrock standard of "evidence-based medical practice." When considering clinical practice guidelines, it is essential that physicians recognize the relative risks and benefits of such documents. If done properly, they can distill large data sets into actionable clinical recommendations. However, there is a long history of clinical practice guidelines that have later been found to be deficient, resulting in wasted medical resources, failure to achieve desired benefits, and, at times, substantial harm to patients.[87]

[87] See S. H. Woolf et al., Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines, 318 BMJ 527 (1999).

82. In 2009, the Endocrine Society published clinical guidelines for the treatment of patients with persistent gender dysphoria.[88] The recommendations include temporary suppression of pubertal development of children with GnRH agonists followed by hormonal treatments to induce the development of secondary sexual traits consistent with one's gender identity. In developing these guidelines, the authors assessed the quality of evidence supporting the recommendations made with use of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system for rating clinical guidelines. As stated in the Endocrine Society publication, "the strength of recommendations and the quality of evidence was low or very low."[89] According to the GRADE system, low recommendations indicate that "[f]urther research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate."[90] Very low recommendations mean that "any estimate of effect is very uncertain."[91]

83. The Endocrine Society published an updated set of guidelines in September 2017.[92] Those guidelines show that all recommendations as to "affirming"

[88] See W. C. Hembree et al. (2009), Endocrine Treatment of Transsexual Persons, 94 J. Clin. Endocrinol. & Metabol. at 3132, 3132-54.
[89] *Id.* at 3132.
[90] G. H. Guyatt et al., GRADE: an emerging consensus on rating quality of evidence and strength of recommendations, 336 BMJ 924, 926 (2008).
[91] *Id.*
[92] See W. C. Hembree et al., Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline, 102 J. Clin. Endocrinol. & Metabol.,

treatment of adolescents are supported by low or very low-quality evidence.[93] Despite this low-quality evidence in this document, strong recommendations are frequently made on the basis of the "values and preferences" of either the Endocrine Society or the patient.[94] For instance, the Endocrine Society's recommendations expressly place "a lower value on avoiding potential harm from early pubertal suppression."[95]

84. Dr. Guyatt, a co-developer of the GRADE system, "found 'serious problems' with the Endocrine Society guidelines, noting that the systematic reviews didn't look at the effect of the interventions on gender dysphoria itself, arguably 'the most important outcome.'"[96] He also criticized the Endocrine Society guidelines for pairing strong recommendations with weak evidence, explaining that such practice is discouraged "except under very specific circumstances."[97]

3869, 3869-3903 (2017). See also Corrigendum for "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline," 103 J. Clin. Endocrinol. & Metabol. 2758 (July 2018) ("Endocrine Society Clinical Practice Guideline"); Corrigendum for "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline," 103 J. Clin. Endocrinol. & Metabol. 699 (Feb. 2018).

[93] J. Block, Gender dysphoria in young people is rising — and so is professional disagreement, 380 BMJ 382, at *2 (2023). See also W. C. Hembree et al. (2017), Endocrine Society Clinical Practice Guideline, 102 J. Clin. Endocrinol. & Metab. at 3869-3903.

[94] See, e.g., W. C. Hembree et al. (2017), Endocrine Society Clinical Practice Guideline, 102 J. Clin. Endocrinol. & Metab., at 3872-73, 3881, 3894.

[95] *Id.* at 3881.

[96] J. Block (2023), Gender dysphoria in young people is rising, 380 BMJ 382, at *2-*3.

[97] *Id.* at *3.

85. The Endocrine Society guidelines state that "[w]eak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action."[98] These values and preferences include the desire of the individual seeking gender-affirming medical interventions, who may be operating under an *a priori* presumption (encouraged by the Endocrine Society's "strong recommendations") that these will lead to improved mental health. As detailed throughout this declaration, the existing data do not support this presumption. Instead, the existing data substantiate Dr. Guyatt's concerns as summarized by J. Block:

> For Guyatt, claims of certainty represent both the success and failure of the evidence-based medicine movement. "Everybody now has to claim to be evidence based" in order to be taken seriously, he says—that's the success. But people "don't particularly adhere to the standard of what is evidence based medicine—that's the failure." When there's been a rigorous systematic review of the evidence and the bottom line is that "we don't know,'" he says, then "anybody who then claims they do know is not being evidence based."[99]

86. It is highly misleading to imply that the current Endocrine Society guidelines[100] represent the opinions of the Society's 18,000 members. The committee that drafted these guidelines was composed of *less than a dozen* members. The guidelines were never submitted to the entire Endocrine Society membership for

[98] W. C. Hembree et al. (2017), Endocrine Society Clinical Practice Guideline, 102 J. Clin. Endocrinol. & Metab., at 3872-73, 3885.
[99] J. Block (2023), Gender dysphoria in young people is rising, 380 BMJ 382, at *4.
[100] W. C. Hembree et al. (2017), Endocrine Society Clinical Practice Guideline, 102 J. Clin. Endocrinol. & Metab., at 3872.

comment and approval prior to publication. They also did not undergo external review. Such methodologies are common in association "statements" and "endorsement"; they are not scientific or generally reliable.

CONCLUSIONS

87. The use of puberty blockers to suppress puberty for the purpose of treating gender dysphoria carries risks that are not present when puberty blockers are used to treat precocious puberty.

88. There are no long-term, peer-reviewed, published, reliable, and valid research studies documenting that the use of puberty blockers to treat gender dysphoria is "reversible."

89. Evidence suggests that the use of puberty blockers to treat gender dysphoria carries risks of infertility, decreased bone density, and decreased height.

90. It is unknown what effect the use of puberty blockers to treat gender dysphoria has on brain maturation.

91. The use of cross-sex hormones to treat gender dysphoria carries risks that are not present when those hormones are given based on endogenous profiles (*e.g.*, testosterone to males and estrogen to females).

92. Evidence suggests that the use of cross-sex hormones to treat gender dysphoria carries risks of sterility.

93. The use of gender affirming hormones to treat gender dysphoria potentially carry risks of liver disease, thrombosis, cardiovascular disease, breast cancer, and high blood pressure.

94. The use of non-physiological levels of estrogen in males has been shown to increase the risk of thromboembolic stroke above the incidence observed in females.

95. The committee that developed the Endocrine Society gender-dysphoria guidelines relied on low-quality scientific evidence in making strong treatment recommendations and failed to adequately review the scientific evidence pertaining to long-term risk of medical interventions to affirm sex-discordant gender identity.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on May 26, 2023.

Paul W. Hruz, M.D., Ph.D.

Exhibit A

Curriculum Vitae

Date: 5/26/2023
Name: Paul W. Hruz, M.D., Ph.D.

Contact Information

Office:	Phone: 314-286-2797 Fax: 314-286-2892
Mail:	Washington University in St. Louis School of Medicine Department of Pediatrics Endocrinology and Diabetes 660 South Euclid Avenue St Louis MO 63110
Email:	Office: hruz_p@wustl.edu

Present Position

Associate Professor of Pediatrics, Endocrinology and Diabetes
Associate Professor of Pediatrics, Cell Biology & Physiology

Education

1987	BS, Chemistry, Marquette University, Milwaukee, WI
1993	PhD, Biochemistry, Medical College of Wisconsin, Milwaukee, WI Elucidation of Structural, Mechanistic, and Regulatory Elements in 3-Hydroxy-3-Methlyglutaryl-Coenzyme A Lyase, Henry Miziorko
1994	MD, Medicine, Medical College of Wisconsin, Milwaukee, WI
1994 - 1997	Pediatric Residency, University of Washington, Seattle, Washington
1997 - 2000	Pediatric Endocrinology Fellowship, Washington University, Saint Louis, MO
2017	Certification in Healthcare Ethics, National Catholic Bioethics Center, Philadelphia, PA

Academic Positions / Employment

1996 - 1997	Locum Tenens Physician, Group Health of Puget Sound Eastside Hospital, Group Health of Puget Sound Eastside Hospital, Seattle , WA
2000 - 2003	Instructor in Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO
2003 - 2011	Assistant Professor of Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO
2004 - 2011	Assistant Professor of Pediatrics, Cell Biology & Physiology, Washington University in St. Louis, St. Louis, MO
2011 - Pres	Associate Professor of Pediatrics, Cell Biology & Physiology, Washington University in St. Louis, St. Louis, MO

2011 - Pres	Associate Professor of Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO
2012 - 2017	Division Chief, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO

Clinical Title and Responsibilities

	General Pediatrician, General Pediatric Ward Attending: 2-4 weeks per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Endocrinology Night Telephone Consult Service: Average of 2-6 weeks/per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Inpatient Endocrinology Consult Service: 3-6 weeks per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Outpatient Endocrinology Clinic: Approximately 150 patient visits per month, St. Louis Children's Hospital

Teaching Title and Responsibilities

2009 - Pres	Lecturer, Markey Course-Diabetes Module
2008 – 2016	Fellowship Program Director- Pediatric Endocrinology and Diabetes
2020 - 2020	Facilitator, Reading Elective-Interdisciplinary/Miscellaneous Course #M80-800, Washington University School of Medicine
2019 – Pres	Associate Fellowship Program Director- Pediatric Endocrinology and Diabetes

University, School of Medicine and Hospital Appointments and Committees

University

2012 - 2020	Disorders of Sexual Development Multidisciplinary Care Program

School of Medicine

2013 - 2020	Molecular Cell Biology Graduate Student Admissions Committee
2014 - Pres	Research Consultant, ICTS Research Forum - Child Health

Hospital

2000 - Pres	Attending Physician, St. Louis Children's Hospital

Medical Licensure and Certifications

1997 - Pres	Board Certified in General Pediatrics
2000 - Pres	MO Stae License #2000155004
2001 - Pres	Board Certified in Pediatric Endocrinology & Metabolism

Honors and Awards

1987	National Institute of Chemists Research and Recognition Award
1987	Phi Beta Kappa
1987	Phi Lambda Upsilon (Honorary Chemical Society)
1988	American Heart Association Predoctoral Fellowship Award

1994	Alpha Omega Alpha
1994	Armond J. Quick Award for Excellence in Biochemistry
1994	NIDDK/Diabetes Branch Most Outstanding Resident
1998	Pfizer Postdoctoral Fellowship Award
2002	Scholar, Child Health Research Center of Excellence in Developmental Biology at Washington University
2013	Julio V Santiago, M.D. Scholar in Pediatrics
2017	Redemptor Hominis Award for Outstanding Contributions to the Study of Bioethics
2018	Eli Lilly Outstanding Contribution to Drug Discovery: Emerging Biology Award
2018	Scholar-Innovator Award, Harrington Discovery Institute
2021	Linacre Award

Editorial Responsibilities

Editorial Ad Hoc Reviews

	AIDS
	AIDS Research and Human Retroviruses
	American Journal of Pathology
	American Journal of Physiology
	British Journal of Pharmacology
	Circulation Research
	Clinical Pharmacology & Therapeutics
	Comparative Biochemistry and Physiology
	Diabetes
	Experimental Biology and Medicine
	Future Virology
	Journal of Antimicrobial Chemotherapy
	Journal of Clinical Endocrinology & Metabolism
	Journal of Molecular and Cellular Cardiology
	Obesity Research
2000 - Pres	Journal of Biological Chemistry
2013 - Pres	PlosOne
2016 - Pres	Scientific Reports
2018 - Pres	Nutrients

Editorial Boards

2014 - 2015	Endocrinology and Metabolism Clinics of North America

National Panels, Committees

2017 - Pres	Consultant, Catholic Health Association
2021 - Pres	Consulting Fellow, National Catholic Bioethics Center

National Boards

2020 - Pres	WU ICTS Clinical and Translational Research Funding Program (CTRFP) Review Committee

Professional Societies and Organizations

American Diabetes Association

Endocrine Society

Pediatric Endocrine Society

Major Invited Professorships and Lectures

2002	Pediatric Grand Rounds, St. Louis Children's Hospital, St Louis, MO
2004	National Disease Research Interchange, Human Islet Cell Research Conference, Philadelphia, PA
2004	NIDA-NIH Sponsored National Meeting on Hormones, Drug Abuse and Infections, Bethesda, MD
2005	Endocrine Grand Rounds, University of Indiana, Indianapolis, IN
2005	The Collaborative Institute of Virology, Complications Committee Meeting, Boston, MA
2006	Metabolic Syndrome Advisory Board Meeting, Bristol-Meyers Squibb, Pennington, NJ
2007	American Heart Association and American Academy of HIV Medicine State of the Science Conference: Initiative to Decrease Cardiovascular Risk and Increase Quality of Care for Patients Living with HIV/AIDS, Chicago, IL
2007	Minority Access to Research Careers Seminar, University of Arizona, Tucson, AZ
2007	MSTP Annual Visiting Alumnus Lecture, Medical College of Wisconsin , Milwaukee, WI
2007	Pediatric Grand Rounds, St Louis Children’s Hospital, St Louis, MO
2008	Division of Endocrinology, Diabetes and Nutrition Grand Rounds, Boston University, Boston, MA
2009	Pediatric Grand Rounds, St Louis Children's Hospital, St. Louis, MO
2010	American Diabetes Association Scientific Sessions, Symposium Lecture Orlando, FL
2010	School of Biological Sciences Conference Series, University of Missouri Kansas City, Kansas City, MO
2011	Life Cycle Management Advisory Board Meeting, Bristol-Myers Squibb,, Chicago, IL
2013	Pediatric Grand Rounds, St Louis Children's Hospital, ST LOUIS, MO
2013	Clinical Practice Update Lecture, St Louis Children's Hospital, St Louis, MO
2014	Pediatric Academic Societies Meeting,, Vancouver, Canada
2014	American Diabetes Association 74th Scientific Sessions, , San Francisco, CA
2017	Division of Pediatric Endocrinology Metabolism Rounds, University of Michigan, Ann Arbor, MI
2017	Catholic Medical Association National Conference, Denver, CO
2018	Obstetrics, Gynecology & Women's Health Grand Rounds, Saint Louis University, St. Louis, MO
2018	Medical Grand Rounds, Sindicato Médico del Uruguay, Montevideo, Uraquay
2018	Internal Medicine Grand Rounds, Texas Tech , Lubbock, TX
2019	Veritas Center for Ethics in Public Life Conference, Franciscan University, Steubenville, OH
2019	MaterCare International Conference, Rome, Italy
2019	Child Health Policy Forum, Notre Dame University, South Bend , IN

2021 Obstetrics & Gynecology Grand Rounds, University of Tennessee, Knoxville , TN
2022 The World Federation of Catholic Medical Associations (*FIAMC*), Rome, Italy

Consulting Relationships and Board Memberships

1996 - 2012 Consultant, Bristol Myers Squibb
1997 - 2012 Consultant, Gilead Sciences

Research Support

Completed Governmental Support

2001 - 2006 K-08 A149747, NIH
Mechanism of GLUT4 Inhibition by HIV Protease Inhibitors
Role: Principal Investigator

2007 - 2012 R01
Mechanisms for Altered Glucose Homeostasis During HAART
Role: Principal Investigator
Total cost: $800,000.00

2009 - 2011 R01 Student Supp
Mechanisms for Altered Glucose Homeostasis During HAART
Role: Principal Investigator
Total cost: $25,128.00

2009 - 2014 R01
Direct Effects of Antiretroviral Therapy on Cardiac Energy Homeostasis
Role: Principal Investigator
Total cost: $1,250,000.00

2017 - 2019 R-21 1R21AI130584 , National Institutes of Health
SELECTIVE INHIBITION OF THE P. FALCIPARUM GLUCOSE TRANSPORTER PFHT
Role: Principal Investigator
Total cost: $228,750.00

Completed Non-Governmental Support

2015 Novel HIV Protease Inhibitors and GLUT4
Role: Principal Investigator

2008 - 2011 II
Insulin Resistance and Myocardial Glucose Metabolism in Pediatric Heart Failure
Role: Co-Investigator
PI: Hruz
Total cost: $249,999.00

2009 - 2012 Research Program
Regulation of GLUT4 Intrinsic Activity
Role: Principal Investigator
Total cost: $268,262.00

2010 - 2011 Protective Effect of Saxagliptin on a Progressive Deterioration of Cardiovascular Function
Role: Principal Investigator

2012 - 2015 II
Solution-State NMR Structure and Dynamics of Facilitative Glucose Transport Proteins
Role: Principal Investigator
Total cost: $375,000.00

2017 - 2020 Prevention And Treatment Of Hepatic Steatosis Through Selective Targeting Of GLUT8
Role: Co-Principal Investigator
PI: DeBosch
Total cost: $450,000.00

2017 - 2021 Matching Micro Grant
Novel Treatment of Fatty Liver Disease (CDD/LEAP)
Role: Principal Investigator
Total cost: $68,500.00

2018 - 2021 LEAP Innovator Challenge
Novel Treatment of Fatty Liver Disease
Role: Principal Investigator
Total cost: $68,500.00

2019 - 2021 Scholar-Innovator Award HDI2019-SI-4555 , Harrington Foundation
Novel Treatment of Non-Alcoholic Fatty Liver Disease
Role: Principal Investigator
Total cost: $379,000.00

Current Governmental Support

2021 - 2025 R-01 DK126622 (Co-investigator), 8/25/2021-7/31/2025, NIH-NIDDK, , NIH
Leveraging glucose transport and the adaptive fasting response to modulate hepatic metabolism
Role: Co-Investigator
PI: DeBosch

Trainee/Mentee/Sponsorship Record

2002 - 2002 Nishant Raj- Undergraduate Student, Other
Study area: Researcher

2002 - 2010 Joseph Koster, PhD, Postdoctoral Fellow
Study area: Researcher

2003 - 2004 Johann Hertel, Medical Student
Study area: Research
Present position: Assistant Professor, University of North Carolina, Chapel Hill, NC

2003 - 2003 John Paul Shen, Medical Student
Study area: Research

2004 - 2005 Carl Cassel- High School Student, Other
Study area: Research

2004 - 2004 Christopher Hawkins- Undergraduate Student, Other
Study area: Researcher

2004 - 2004 Kaiming Wu- High School Student, Other
Study area: Research

2005 - 2005 Helena Johnson, Graduate Student

2005 - 2005 Jeremy Etzkorn, Medical Student
Study area: Researcher

2005 - 2005 Dominic Doran, DSc, Postdoctoral Fellow
Study area: HIV Protease Inhibitor Effects on Exercize Tolerance

2006 - 2006 Ramon Jin, Graduate Student
Study area: Research

2006 - 2006 Taekyung Kim, Graduate Student
Study area: Research

2007 - 2007 Jan Freiss- Undergraduate Student, Other
Study area: Researcher

2007 - 2008 Kai-Chien Yang, Graduate Student
Study area: Research
Present position: Postdoctoral Research Associate, University of Chicago

2007 - 2007 Paul Buske, Graduate Student
Study area: Research

2007 - 2007 Randy Colvin, Medical Student
Study area: Researcher

2008 - 2011 Arpita Vyas, MD, Clinical Fellow
Study area: Research
Present position: Assistant Professor, Michigan State University, Lansing MI

2008 - 2009 Candace Reno, Graduate Student
Study area: Research
Present position: Research Associate, University of Utah

2008 - 2012 Dennis Woo- Undergraduate Student, Other
Study area: Researcher
Present position: MSTP Student, USC, Los Angeles CA

2008 - 2008 Temitope Aiyejorun, Graduate Student
Study area: Research

2009 - 2009 Anne-Sophie Stolle- Undergraduate Student, Other
Study area: Research

2009 - 2009 Matthew Hruz- High School Student, Other
Study area: Research
Present position: Computer Programmer, Consumer Affairs, Tulsa OK

2009 - 2009 Stephanie Scherer, Graduate Student
Study area: Research

2010 - 2014 Lauren Flessner, PhD, Postdoctoral Fellow
Present position: Instructor, Syracuse University

2010 - 2010 Constance Haufe- Undergraduate Student, Other
Study area: Researcher

2010 - 2011 Corinna Wilde- Undergraduate Student, Other
Study area: Researcher

2010 - 2010 Samuel Lite- High School Student, Other
Study area: Research

2011 - 2016 Thomas Kraft, Graduate Student
Study area: Glucose transporter structure/function
Present position: Postdoctoral Fellow, Roche, Penzberg, Germany

2011 - 2011 Amanda Koenig- High School Student, Other
Study area: Research

2011 - 2012 Lisa Becker- Undergraduate Student, Other

2011 - 2011 Melissa Al-Jaoude- High School Students, Other

2019 Ava Suda, Other, Pre-med

Bibliography

A. Journal Articles

1. Hruz PW, Narasimhan C, Miziorko HM. 3-Hydroxy-3-methylglutaryl coenzyme A lyase: affinity labeling of the Pseudomonas mevalonii enzyme and assignment of cysteine-237 to the active site. *Biochemistry*. 1992;31(29):6842-7. PMID:1637819
2. Hruz PW, Miziorko HM. Avian 3-hydroxy-3-methylglutaryl-CoA lyase: sensitivity of enzyme activity to thiol/disulfide exchange and identification of proximal reactive cysteines. *Protein Sci*. 1992;1(9):1144-53. doi:10.1002/pro.5560010908 PMCID:PMC2142181 PMID:1304393
3. Mitchell GA, Robert MF, Hruz PW, Wang S, Fontaine G, Behnke CE, Mende-Mueller LM, Schappert K, Lee C, Gibson KM, Miziorko HM. 3-Hydroxy-3-methylglutaryl coenzyme A lyase (HL). Cloning of human and chicken liver HL cDNAs and characterization of a mutation causing human HL deficiency. *J Biol Chem*. 1993;268(6):4376-81. PMID:8440722
4. Hruz PW, Anderson VE, Miziorko HM. 3-Hydroxy-3-methylglutaryldithio-CoA: utility of an alternative substrate in elucidation of a role for HMG-CoA lyase's cation activator. *Biochim Biophys Acta*. 1993;1162(1-2):149-54. PMID:8095409
5. Roberts JR, Narasimhan C, Hruz PW, Mitchell GA, Miziorko HM. 3-Hydroxy-3-methylglutaryl-CoA lyase: expression and isolation of the recombinant human enzyme and investigation of a mechanism for regulation of enzyme activity. *J Biol Chem*. 1994;269(27):17841-6. PMID:8027038
6. Hruz PW, Mueckler MM. Cysteine-scanning mutagenesis of transmembrane segment 7 of the GLUT1 glucose transporter. *J Biol Chem*. 1999;274(51):36176-80. PMID:10593902
7. Murata H, Hruz PW, Mueckler M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem*. 2000;275(27):20251-4. doi:10.1074/jbc.C000228200 PMID:10806189
8. Hruz PW, Mueckler MM. Cysteine-scanning mutagenesis of transmembrane segment 11 of the GLUT1 facilitative glucose transporter. *Biochemistry*. 2000;39(31):9367-72. PMID:10924131
9. Hruz PW, Mueckler MM. Structural analysis of the GLUT1 facilitative glucose transporter (review). *Mol Membr Biol*. 2001;18(3):183-93. PMID:11681785
10. Murata H, Hruz PW, Mueckler M. Investigating the cellular targets of HIV protease inhibitors: implications for metabolic disorders and improvements in drug therapy. *Curr Drug Targets Infect Disord*. 2002;2(1):1-8. PMID:12462148
11. Hruz PW, Murata H, Qiu H, Mueckler M. Indinavir induces acute and reversible peripheral insulin resistance in rats. *Diabetes*. 2002;51(4):937-42. PMID:11916910
12. Murata H, Hruz PW, Mueckler M. Indinavir inhibits the glucose transporter isoform Glut4 at physiologic concentrations. *AIDS*. 2002;16(6):859-63. PMID:11919487
13. Koster JC, Remedi MS, Qiu H, Nichols CG, Hruz PW. HIV protease inhibitors acutely impair glucose-stimulated insulin release. *Diabetes*. 2003;52(7):1695-700. PMCID:PMC1403824 PMID:12829635
14. Liao Y, Shikapwashya ON, Shteyer E, Dieckgraefe BK, Hruz PW, Rudnick DA. Delayed hepatocellular mitotic progression and impaired liver regeneration in early growth response-1-deficient mice. *J Biol Chem*. 2004;279(41):43107-16. doi:10.1074/jbc.M407969200 PMID:15265859
15. Shteyer E, Liao Y, Muglia LJ, Hruz PW, Rudnick DA. Disruption of hepatic adipogenesis is associated with impaired liver regeneration in mice. *Hepatology*. 2004;40(6):1322-32. doi:10.1002/hep.20462 PMID:15565660
16. Hertel J, Struthers H, Horj CB, Hruz PW. A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity. *J Biol Chem*. 2004;279(53):55147-52. doi:10.1074/jbc.M410826200 PMCID:PMC1403823 PMID:15496402

17. Yan Q, Hruz PW. Direct comparison of the acute in vivo effects of HIV protease inhibitors on peripheral glucose disposal. *J Acquir Immune Defic Syndr*. 2005;40(4):398-403. PMCID:PMC1360159 PMID:16280693
18. Hruz PW. Molecular Mechanisms for Altered Glucose Homeostasis in HIV Infection. *Am J Infect Dis*. 2006;2(3):187-192. PMCID:PMC1716153 PMID:17186064
19. Turmelle YP, Shikapwashya O, Tu S, Hruz PW, Yan Q, Rudnick DA. Rosiglitazone inhibits mouse liver regeneration. *FASEB J*. 2006;20(14):2609-11. doi:10.1096/fj.06-6511fje PMID:17077279
20. Hruz PW, Yan Q, Struthers H, Jay PY. HIV protease inhibitors that block GLUT4 precipitate acute, decompensated heart failure in a mouse model of dilated cardiomyopathy. *FASEB J*. 2008;22(7):2161-7. doi:10.1096/fj.07-102269 PMID:18256305
21. Hruz PW. HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. *Curr Opin HIV AIDS*. 2008;3(6):660-5. doi:10.1097/COH.0b013e3283139134 PMCID:PMC2680222 PMID:19373039
22. Flint OP, Noor MA, Hruz PW, Hylemon PB, Yarasheski K, Kotler DP, Parker RA, Bellamine A. The role of protease inhibitors in the pathogenesis of HIV-associated lipodystrophy: cellular mechanisms and clinical implications. *Toxicol Pathol*. 2009;37(1):65-77. doi:10.1177/0192623308327119 PMCID:PMC3170409 PMID:19171928
23. Tu P, Bhasin S, Hruz PW, Herbst KL, Castellani LW, Hua N, Hamilton JA, Guo W. Genetic disruption of myostatin reduces the development of proatherogenic dyslipidemia and atherogenic lesions in Ldlr null mice. *Diabetes*. 2009;58(8):1739-48. doi:10.2337/db09-0349 PMCID:PMC2712781 PMID:19509018
24. Guo W, Wong S, Pudney J, Jasuja R, Hua N, Jiang L, Miller A, Hruz PW, Hamilton JA, Bhasin S. Acipimox, an inhibitor of lipolysis, attenuates atherogenesis in LDLR-null mice treated with HIV protease inhibitor ritonavir. *Arterioscler Thromb Vasc Biol*. 2009;29(12):2028-32. doi:10.1161/ATVBAHA.109.191304 PMCID:PMC2783673 PMID:19762785
25. Vyas AK, Koster JC, Tzekov A, Hruz PW. Effects of the HIV protease inhibitor ritonavir on GLUT4 knock-out mice. *J Biol Chem*. 2010;285(47):36395-400. doi:10.1074/jbc.M110.176321 PMCID:PMC2978568 PMID:20864532
26. Gazit V, Weymann A, Hartman E, Finck BN, Hruz PW, Tzekov A, Rudnick DA. Liver regeneration is impaired in lipodystrophic fatty liver dystrophy mice. *Hepatology*. 2010;52(6):2109-17. doi:10.1002/hep.23920 PMCID:PMC2991544 PMID:20967828
27. Hresko RC, Hruz PW. HIV protease inhibitors act as competitive inhibitors of the cytoplasmic glucose binding site of GLUTs with differing affinities for GLUT1 and GLUT4. *PLoS One*. 2011;6(9):e25237. doi:10.1371/journal.pone.0025237 PMCID:PMC3179492 PMID:21966466
28. Vyas AK, Yang KC, Woo D, Tzekov A, Kovacs A, Jay PY, Hruz PW. Exenatide improves glucose homeostasis and prolongs survival in a murine model of dilated cardiomyopathy. *PLoS One*. 2011;6(2):e17178. doi:10.1371/journal.pone.0017178 PMCID:PMC3040766 PMID:21359201
29. Hruz PW, Yan Q, Tsai L, Koster J, Xu L, Cihlar T, Callebaut C. GS-8374, a novel HIV protease inhibitor, does not alter glucose homeostasis in cultured adipocytes or in a healthy-rodent model system. *Antimicrob Agents Chemother*. 2011;55(4):1377-82. doi:10.1128/AAC.01184-10 PMCID:PMC3067185 PMID:21245443
30. Remedi MS, Agapova SE, Vyas AK, Hruz PW, Nichols CG. Acute sulfonylurea therapy at disease onset can cause permanent remission of KATP-induced diabetes. *Diabetes*. 2011;60(10):2515-22. doi:10.2337/db11-0538 PMCID:PMC3178299 PMID:21813803
31. Aerni-Flessner L, Abi-Jaoude M, Koenig A, Payne M, Hruz PW. GLUT4, GLUT1, and GLUT8 are the dominant GLUT transcripts expressed in the murine left ventricle. *Cardiovasc Diabetol*. 2012;11:63. doi:10.1186/1475-2840-11-63 PMCID:PMC3416696 PMID:22681646

32. Vyas AK, Aerni-Flessner LB, Payne MA, Kovacs A, Jay PY, Hruz PW. Saxagliptin Improves Glucose Tolerance but not Survival in a Murine Model of Dilated Cardiomyopathy. *Cardiovasc Endocrinol*. 2012;1(4):74-82. doi:10.1097/XCE.0b013e32835bfb24 PMCID:PMC3686315 PMID:23795310
33. Hresko RC, Kraft TE, Tzekov A, Wildman SA, Hruz PW. Isoform-selective inhibition of facilitative glucose transporters: elucidation of the molecular mechanism of HIV protease inhibitor binding. *J Biol Chem*. 2014;289(23):16100-16113. doi:10.1074/jbc.M113.528430 PMCID:PMC4047383 PMID:24706759
34. Mishra RK, Wei C, Hresko RC, Bajpai R, Heitmeier M, Matulis SM, Nooka AK, Rosen ST, Hruz PW, Schiltz GE, Shanmugam M. In Silico Modeling-based Identification of Glucose Transporter 4 (GLUT4)-selective Inhibitors for Cancer Therapy. *J Biol Chem*. 2015;290(23):14441-53. doi:10.1074/jbc.M114.628826 PMID:25847249
35. Kraft TE, Hresko RC, Hruz PW. Expression, purification, and functional characterization of the insulin-responsive facilitative glucose transporter GLUT4. *Protein Sci*. 2015. doi:10.1002/pro.2812 PMID:26402434
36. Kraft TE, Armstrong C, Heitmeier MR, Odom AR, Hruz PW. The Glucose Transporter PfHT1 Is an Antimalarial Target of the HIV Protease Inhibitor Lopinavir. *Antimicrob Agents Chemother*. 2015;59(10):6203-9. doi:10.1128/AAC.00899-15 PMCID:PMC4576095 PMID:26248369
37. DeBosch BJ, Heitmeier MR, Mayer AL, Higgins CB, Crowley JR, Kraft TE, Chi M, Newberry EP, Chen Z, Finck BN, Davidson NO, Yarasheski KE, Hruz PW, Moley KH. Trehalose inhibits solute carrier 2A (SLC2A) proteins to induce autophagy and prevent hepatic steatosis. *Sci Signal*. 2016;9(416):ra21. doi:10.1126/scisignal.aac5472 PMID:26905426
38. Hresko RC, Kraft TE, Quigley A, Carpenter EP, Hruz PW. Mammalian Glucose Transporter Activity is Dependent upon Anionic and Conical Phospholipids. *J Biol Chem*. 2016. doi:10.1074/jbc.M116.730168 PMID:27302065
39. Kraft TE, Heitmeier MR, Putanko M, Edwards RL, Ilagan MX, Payne MA, Autry JM, Thomas DD, Odom AR, Hruz PW. A Novel Fluorescence Resonance Energy Transfer-Based Screen in High-Throughput Format To Identify Inhibitors of Malarial and Human Glucose Transporters. *Antimicrob Agents Chemother*. 2016;60(12):7407-7414. PMCID:PMC5119023 PMID:27736766
40. Mayer AL, Higgins CB, Heitmeier MR, Kraft TE, Qian X, Crowley JR, Hyrc KL, Beatty WL, Yarasheski KE, Hruz PW, DeBosch BJ. SLC2A8 (GLUT8) is a mammalian trehalose transporter required for trehalose-induced autophagy. *Sci Rep*. 2016;6:38586. PMCID:PMC5138640 PMID:27922102
41. Edwards RL, Brothers RC, Wang X, Maron MI, Ziniel PD, Tsang PS, Kraft TE, Hruz PW, Williamson KC, Dowd CS, John ARO. MEPicides: potent antimalarial prodrugs targeting isoprenoid biosynthesis. *Sci Rep*. 2017;7(1):8400. PMCID:PMC5567135 PMID:28827774
42. Wei C, Bajpai R, Sharma H, Heitmeier M, Jain AD, Matulis SM, Nooka AK, Mishra RK, Hruz PW, Schiltz GE, Shanmugam M. Development of GLUT4-selective antagonists for multiple myeloma therapy. *Eur J Med Chem*. 2017;139:573-586. PMCID:PMC5603412 PMID:28837922
43. Wei C, Heitmeier M, Hruz PW, Shanmugam M. Evaluating the Efficacy of GLUT Inhibitors Using a Seahorse Extracellular Flux Analyzer. *Methods Mol Biol*. 2018;1713:69-75. PMID:29218518
44. Heitmeier MR, Payne MA, Weinheimer C, Kovacs A, Hresko RC, Jay PY, Hruz PW. Metabolic and Cardiac Adaptation to Chronic Pharmacologic Blockade of Facilitative Glucose Transport in Murine Dilated Cardiomyopathy and Myocardial Ischemia. *Sci Rep*. 2018;8(1):6475. PMID:29691457
45. Zhang Y, Higgins CB, Mayer AL, Mysorekar IU, Razani BB, Graham MJ, Hruz PW, DeBosch BJ. TFEB-dependent Induction of Thermogenesis by the Hepatocyte SLC2A Inhibitor Trehalose. *Autophagy*. 2018. PMID:29996716

46. Emfinger CH, Yan Z, Welscher A, Hung P, McAllister W, Hruz PW, Nichols CG, Remedi MS. Contribution of systemic inflammation to permanence of K_{ATP}-induced neonatal diabetes in mice. *Am J Physiol Endocrinol Metab*. 2018;315(6):E1121-E1132. PMCID:PMC6336961 PMID:30226997
47. Heitmeier MR, Hresko RC, Edwards RL, Prinsen MJ, Ilagan MXG, Odom John AR, Hruz PW. Identification of druggable small molecule antagonists of the Plasmodium falciparum hexose transporter PfHT and assessment of ligand access to the glucose permeation pathway via FLAG-mediated protein engineering. *PLoS One*. 2019;14(5):e0216457. PMCID:PMC6508677 PMID:31071153
48. Hruz PW. Deficiencies in Scientific Evidence for Medical Management of Gender Dysphoria. *Linacre Q*. 2020;87(1):34-42. PMCID:PMC7016442 PMID:32431446
49. Zhang Y, Shaikh N, Ferey JL, Wankhade UD, Chintapalli SV, Higgins CB, Crowley JR, Heitmeier MR, Stothard AI, Mihi B, Good M, Higashiyama T, Swarts BM, Hruz PW, Shankar K, Tarr PI, DeBosch BJ. Lactotrehalose, an Analog of Trehalose, Increases Energy Metabolism Without Promoting Clostridioides difficile Infection in Mice. *Gastroenterology*. 2020;158(5):1402-1416.e2. PMCID:PMC7103499 PMID:31838076
50. Malone WJ, Hruz PW, Mason JW, Beck S. Letter to the Editor from William J. Malone: "Proper Care of Transgender and Gender Diverse Persons in the Setting of Proposed Discrimination: A Policy Perspective". *J Clin Endocrinol Metab*. 2021. PMID:33772300
51. McMillin SL, Evans PL, Taylor WM, Weyrauch LA, Sermersheim TJ, Welc SS, Heitmeier MR, Hresko RC, Hruz PW, Koumanov F, Holman GD, Abel ED, Witczak CA. Muscle-Specific Ablation of Glucose Transporter 1 (GLUT1) Does Not Impair Basal or Overload-Stimulated Skeletal Muscle Glucose Uptake. *Biomolecules*. 2022;12(12):1734. PMID: 36551162; PMCID: PMC9776291.
52. Tayebi N, Leon-Ricardo B, McCall K, Mehinovic E, Engelstad K, Huynh V, Turner TN, Weisenberg J, Thio LL, Hruz P, Williams RSB, De Vivo DC, Petit V, Haller G, Gurnett CA. Quantitative determination of SLC2A1 variant functional effects in GLUT1 deficiency syndrome. Ann Clin Transl Neurol. 2023 May;10(5):787-801. doi: 10.1002/acn3.51767. Epub 2023 Mar 31. PMID: 37000947; PMCID: PMC10187726.

C2. Chapters

1. Henderson KE, Baranski TJ, Bickel PE, Clutter PE, Clutter WE, McGill JB. Endocrine Disorders in HIV/AIDS. In: *The Washington Manual Endocrinology Subspecialty Consult* Philadelphia, PA; 2008:321-328.
2. Paul W Hruz. Medical Approaches to Alleviating Gender Dysphoria In: Edward J Furton, eds. *Transgender Issues in Catholic Health Care* Philadelphia PA; 2021:1-42.
3. Cara Buskmiller and Paul Hruz. A Biological Understanding of Man and Woman In: John Finley, eds. *Sexual Identity: The Harmony of Philosophy, Science, and Revelation* Steubenville OH; 2022:Chapter 2, pp 65-103.

C4. Invited Publications

1. Grunfeld C, Kotler DP, Arnett DK, Falutz JM, Haffner SM, Hruz P, Masur H, Meigs JB, Mulligan K, Reiss P, Samaras K, Working Group 1. Contribution of metabolic and anthropometric abnormalities to cardiovascular disease risk factors. *Circulation*. 2008;118(2):e20-8. PMCID: PMC3170411 PMID: 18566314
2. Hruz PW. HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. *Curr Opin HIV AIDS*. 2008;3(6):660-5. PMCID: PMC2680222 PMID: 19373039

3. Hruz PW. Molecular mechanisms for insulin resistance in treated HIV-infection. *Best Pract Res Clin Endocrinol Metab*. 2011;25(3):459-68. PMCID: PMC3115529 PMID: 21663839
4. Hruz PW. HIV and endocrine disorders. *Endocrinol Metab Clin North Am*. 2014;43(3): xvii–xviii. PMID: 25169571
5. Hruz PW. Commentary. *Clin Chem*. 2015;61(12):1444. PMID: 26614228
6. Hruz PW, Mayer LS, and McHugh PR. Growing Pains: Problems with Pubertal Suppression in Treating Gender Dysphoria *The New Atlantis*. 2017;52:3-36.
7. Hruz, PW. The Use of Cross-Sex Steroids in Treating Gender Dysphoria *Natl Cathol Bioeth Q*. 2018;17(4):1-11.
8. Hruz, PW. Experimental Approaches to Alleviating Gender Dysphoria in Children *Nat Cathol Bioeth Q*. 2019;19(1):89-104.

Expert Witness Testimony

2009 Rosas v. Astrazeneca

2012 O'Connor v. Stamford

2016 Carcaño et al. v. Patrick McCrory (United States District Court, M.D. North Carolina)

2016 Jane Doe v. Board of Education of the Highland School District (United States District Court For the Southern District of Ohio Eastern Division, Case No. 2:16-CV-, 524)

2017 Ward v. Janssen (Circuit Court of St Louis, Division 16, MO, Case No. 1522-CC00213-01)

2017 Adams v. St John's School Board (United States District Court For the Middle District of Florida, FL Civil Action No. 3:17-cv-00739-TJCJBT)

2017 Ashton Whitaker v. Kenosha Unified School District (United States District Court Eastern District of Wisconsin, Civ. Action No. 2:16-cv-00943)

2018 Terri Bruce v. State of South Dakota (The United States District Court District of South Dakota Western Division, Case No. 17-5080)

2019 Cause DF-15-09887-SD of the 255th Judicial Circuit of Dallas County, TX regarding the dispute between J.A. D.Y. and J.U. D.Y., Children

2021 Kadel vs. Falwell (The United States District Court For The Middle District Of North Carolina, Case No.: 1:19-cv-272-LCB-LPA)

2022 Brandt v Rutledge (The United States District Court Eastern District of Arkansas Central Division, Case No. 4:21-CV-00450-JM)

2022 Eknes-Tucker vs Ivey (United States District Court Middle District of Alabama Northern Division, Case 2:22-cv-00184-LCB-SRW)

2022 D.H. et al. v. Snyder (United States District Court For the District Court of Arizona, Case No. 4:20-cv-00335-SHR)